(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

10/521402

(43) International Publication Date
29 January 2004 (29.01.2004)

PCT

(10) International Publication Number
WO 2004/009085 A2

(51) International Patent Classification[7]: A61K 31/4045, 9/20, 9/28

(21) International Application Number: PCT/IB2003/002838

(22) International Filing Date: 17 July 2003 (17.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
759/DEL/2002 19 July 2002 (19.07.2002) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, 110 019 New Delhi, Delhi (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MATHUR, Rajeev, Shankar** [IN/IN]; KD-66, A, Ashok Vihar Phase - 1, 110052 Delhi (IN). **KUMAR, T. Vijaya** [IN/IN]; H. No. 7-150, Main Raod, Chagalamarry, Dist - Kurnool, 518553 Andhra Pradesh (IN). **ROY, Sunilendu, Bhushan** [IN/IN]; Bungalow #7, Row House, Lokpuram, Thane (West), Mumbai, 400601 Maharashtra (IN). **MALIK, Rajiv** [IN/IN]; 6-B, Pocket-B, Gangotri Enclave, Alaknanda, 110019 New Delhi, Delhi (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay. R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/009085 A2

(54) Title: TASTE MASKED SUMATRIPTAN TABLETS AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The technical field of the present invention relates to uncoated, taste masked sumatriptan tablets for oral administration and processes for their preparation. It also relates to wax polished sumatriptan tablets and processes for their preparation.

TASTE MASKED SUMATRIPTAN TABLETS AND PROCESSES FOR THEIR PREPARATION

FIELD OF THE INVENTION

The technical field of the present invention relates to uncoated, taste masked sumatriptan tablets for oral administration and processes for their preparation. It also relates to wax polished sumatriptan tablets and processes for their preparation.

BACKGROUND OF THE INVENTION

Sumatriptan and its acid salts, particularly the succinate salt, are selective 5-hydroxytryptamine-1 (5HT1) agonists and are marketed as oral tablets in strengths of 25 and 50 mg equivalent to sumatriptan, under the trade name Imitrex®. It is indicated for the acute treatment of migraine attacks with or without aura in adults.

Sumatriptan and its physiologically acceptable salts have an unpleasant taste profile and, when administered orally, may intensify the nausea and vomiting associated with migraines. This limits the use of sumatriptan orally, which is considered to be the most widely accepted and convenient route of administration. Successful masking of the unpleasant taste is a key element for patients' acceptance and compliance of an oral dosage form. Prior art researchers have tried various techniques to mask the unpleasant taste of sumatriptan.

For example, PCT application WO 01/37816 discloses a process for the coating of sumatriptan tablet cores and tablets to provide taste masking of the sumatriptan. The process includes spraying a coating solution or suspension of a sugar, a starch, or a mixture of a sugar and a starch, onto tablet cores to obtain coated tablets. There is the proviso that film-forming agents in the suspension or solution are excluded. At page four of the '816 application, the inventors state that the solution or suspension of the coating mixture is sprayed onto the tablet cores in an amount sufficient to cover, e.g., uniform, the surface of the tablet cores. Similarly, U.S. Patent No. 5,863,559 discloses a film coated solid dosage form of sumatriptan that the inventors state has the unpleasant taste substantially eliminated. The dosage form is disclosed as being a film coated tablet that includes a tablet core containing sumatriptan or a pharmaceutically acceptable salt or solvate thereof as active ingredient. The core is

substantially covered with a coating that includes film forming polymers, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose or methylcellulose, and copolymers of methacrylic acid and methyl methacrylate polymers.

In the prior art, a coating over the core tablet has been used to mask the bitter taste of sumatriptan. Though the coating may mask the unpleasant taste, if the thickness and composition of the coating is not properly controlled it may affect the disintegration and dissolution characteristics of the tablet. Further, the coating operation is a highly controlled and costly process. Preferably, film coatings should have good film properties and sufficient tensile strength to withstand the mechanical stresses associated with the processing, packing, transport and storage of the dosage forms. Moreover, the solution of the film-forming polymer must thoroughly wet the surface of the tablet's core and therefore must be finely atomized to spread well. Hence, only low concentrations of viscous film formers such as hydroxypropyl methylcellulose (HPMC) can be employed, and this results in longer processing times and high costs. Additionally, HPMC has other disadvantages, which include the wetting characteristics; adhesiveness to the tablet surface; pigment binding capacity; mechanical properties of the film; hygroscopicity; permeability to water vapor and oxygen; and a difference in disintegration times between film coated tablets and the core.

Similarly, sugar coating of tablet cores is a tedious process, is hygroscopic and requires greater weight build up to effectively taste mask. For conventional dosage forms, it is important that the disintegration of the tablet and the release of the active ingredient are not influenced by the coating itself.

SUMMARY OF THE INVENTION

In one general aspect there is provided a process for preparing an uncoated sumatriptan tablet for oral administration. The process includes the steps of granulating sumatriptan or a physiologically acceptable salt with one or more diluents and/or binders to form granules; mixing the granules with one or more pharmaceutically acceptable excipients to form a mixture; and compressing the mixture to form a tablet.

Embodiments of the process of forming an uncoated sumatriptan tablet may include or more of the following features. For example, the process may further include wax

polishing of the tablet. The wax polishing may include spraying a solution or suspension of wax material onto the tablet and/or sprinkling a powder grade wax onto the tablet. The wax material may be one or more of shellac, modified shellac (opaglos), opaglos II, carnuba wax, bees wax, paraffin wax, and polyethylene glycol, and in particular may be modified shellac (opaglos). The total weight build up of wax polishing solid may be up to about 10% w/w, based on the total weight of the tablet.

Granulating may include dry mixing the one or more diluents and/or binders with sumatriptan and granulating with an aqueous and/or a non-aqueous solvent. The sumatriptan may be granulated with an aqueous and/or a non-aqueous solution or a suspension of one or more diluents and/or binders. The aqueous solvent may include water. The non-aqueous solvent may include one or both of alcohol and isopropyl alcohol.

The physiologically acceptable salt may be one or more of hydrochloride, hydrobromide, sulphate, nitrate, phosphate, formate, mesylate, citrate, benzoate, fumarate, maleate, tartrate and succinate salts, and may in particular be succinate (1:1).

The one or more diluents may be one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners, and in particular may be lactose. The one or more binders may be one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and alginate, and in particular may be hydroxypropyl methylcellulose.

The one or more pharmaceutically acceptable excipients may be one or more of diluents, binders, disintegrants, lubricants, coloring agents, and flavoring agents. The disintegrant may be one or more of low substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium, starch, crystalline cellulose, hydroxypropyl starch, and partially pregelatinized starch, and in particular may be croscarmellose sodium. The lubricant may be one or more of stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose

esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax, and in particular may be one or both of talc and magnesium stearate.

The process may further include granulating and/or mixing a second active pharmaceutical ingredient with the sumatriptan.

In another general aspect there is provided a process for preparing one or more uncoated sumatriptan tablets for oral administration. The process includes the steps of spraying a solution or suspension of sumatriptan or a pharmaceutically acceptable salt in a solvent onto inert cores to form a first layer, blending the core having the first layer with one or more pharmaceutically acceptable excipients to form a blend, and compressing the blend to form an uncoated tablet.

Embodiments of the process may include one or more of the following features. For example, the solution or suspension of sumatriptan in a solvent may further include one or more diluents and/or binders. The process may further include creating a second layer on the cores having a first layer, the second layer including one or more diluents and/or binders.

The process may further include wax polishing the tablet, and polishing the tablet may include sprinkling a fine powder grade of a wax material on the tablet or spraying a solution or suspension of a wax material in organic solvent onto the tablet.

The inert core may include one or more of a sugar sphere, a non-pareil seed, celpheres, or a pharmaceutically acceptable inert insoluble, soluble or swellable material. The pharmaceutically acceptable inert core may include a non-pareil seed. The insoluble inert material may include one or more of sand, silicon dioxide, glass, microcrystalline cellulose, a plastic, and polystyrene. The soluble inert material may include one or more of a sugar, glucose, mannitol, lactose, xylitol, dextrose, and sucrose. The swellable inert material may be hydroxypropyl methylcellulose.

The process may further include spraying and/or blending a second active pharmaceutical ingredient with the sumatriptan.

In another general aspect there is provided a wax polished dosage form of sumatriptan. The dosage form includes sumatriptan or a physiologically acceptable salt; one or more pharmaceutically acceptable carriers or excipients; and a wax polish on the dosage form.

Embodiments of the dosage form may include one or more of the following features. For example, the wax polish may be a wax material. The wax material may be one or more of shellac, modified shellac (opaglos), opaglos II, carnuba wax, bees wax, paraffin wax, polyethylene glycol. The total weight buildup of wax material may be up to 10% w/w, based on the weight of tablet. The one or more pharmaceutically acceptable excipients or carriers may include one or more of diluent, binder, disintegrant, lubricant/glidant, coloring agent and flavoring agent. The wax polished dosage form of sumatriptan may further include a second active pharmaceutical ingredient in the dosage form.

In another general aspect, an uncoated, wax polished sumatriptan tablet includes a tablet core that includes about 10-200 mg of sumatriptan or a physiologically acceptable salt and one or more pharmaceutically acceptable carriers or excipients, and a wax polish on the tablet core. The wax polish includes an amount of from about 2 to 10% weight/weight of the tablet.

In another general aspect, there is provided an uncoated, taste-masked sumatriptan tablet for oral administration that includes of an intragranular portion and an extragranular portion. The intragranular portion includes granules of sumatriptan or a pharmaceutically acceptable salt and one or more diluents and/or binders present in a sufficient amount to cause taste-masking of the sumatriptan or pharmaceutically acceptable salt. The extragranular portion includes one or more pharmaceutically acceptable excipients around the intragranular granules.

Embodiments of the uncoated, taste-masked sumatriptan tablet for oral administration may include one or more of the following features. For example, the one or more diluents and/or binders in the intragranular portion may completely encapsulate the sumatriptan or acceptable physiological salt or may substantially encapsulate the sumatriptan or acceptable physiological salt.

The intragranular portion and/or the extragranular portion may further include a second active pharmaceutical ingredient.

In another general aspect there is provided a method of treating or prophylactically treating a human suffering from a migraine condition. The method includes orally administering a wax polished dosage form of sumatriptan. The oral dosage form includes sumatriptan or a physiologically acceptable salt and a pharmaceutically acceptable carrier or excipient; one or more pharmaceutically acceptable carriers or excipients; and a wax polish on the dosage form.

In another general aspect there is provided a method of treating or prophylactically treating a human suffering from a migraine condition. The method includes orally administering an uncoated, taste-masked tablet of sumatriptan that includes an intragranular portion and an extragranular portion. The intragranular portion includes granules of sumatriptan or a pharmaceutically acceptable salt and one or more diluents and/or binders present in a sufficient amount to cause taste-masking of the sumatriptan or pharmaceutically acceptable salt. The extragranular portion includes one or more pharmaceutically acceptable excipients around the intragranular granules.

Embodiments of the method may include one or more of the following features. For example, the tablet may include about 10 mg to 200 mg of sumatriptan. The intragranular portion and/or the extragranular portion may further include a second active pharmaceutical ingredient.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

DETAILED DESCRIPTION

Based on the above discussion of the prior art, the inventors recognized a need for a simpler and less expensive approach to masking the bitter taste of sumatriptan. Acting on this recognition, the inventors have now discovered a simple and economical process which effectively masks the unpleasant taste of sumatriptan without the need for any type of

coating. Therefore, in one aspect there is provided a process for preparing an uncoated tablet for oral administration which effectively masks the taste of sumatriptan. In particular, the inventors have now discovered that taste masking properties can be imparted on the dosage form by granulating sumatriptan with one or more diluents and/or binders, mixing the granulated sumatriptan granules with other pharmaceutically acceptable excipients, and compressing to form a tablet. Alternatively, the granules can be filled into a capsule with pharmaceutically acceptable excipients to form a sumatriptan capsule.

The granulation may be carried out by dry mixing the one or more diluents and/or binders with sumatriptan and granulating with an aqueous and/or a non-aqueous solvent. Alternatively, sumatriptan may be granulated with an aqueous and/or a non-aqueous solution/suspension of one or more diluents and/or binders. The aqueous solvent may be, for example, water, and the non-aqueous solvent may be, for example, alcohol or isopropyl alcohol.

The sumatriptan granules may be mixed with other pharmaceutically acceptable excipients and filled into a capsule or compressed to form a tablet. The tablet or capsule prepared above optionally may further be polished with a waxy material by sprinkling a fine powder grade of wax material, or spraying a solution/suspension of wax material in organic solvent, over the tablet or capsule. Polishing may be performed in airless spray equipment followed by air-drying in the spray equipment itself, or tray drying.

The processes described herein avoid a coating step and thereby reduce the processing time and costs associated with coating. Granulation with the one or more diluents and/or binders provides a uniform or a substantially uniform layer or encapsulation over or around the individual sumatriptan particles and thereby masks the unpleasant taste associated with sumatriptan. Nonetheless, optional wax polishing instead of a conventional coating may further provide additional taste masking, less tablet to tablet picking, good stability on storage, and aesthetic appeal to the tablet. It also reduces dust formation, which occurs during packaging of the tablets. Moreover, absence of any coating over the tablets helps to achieve the desired disintegration and dissolution characteristics without failure.

As used herein, the term "Sumatriptan" includes sumatriptan and its pharmaceutically acceptable salts. Such suitable salts include salts of inorganic or organic acids such as

hydrochloride, hydrobromide, sulphate, nitrate, phosphate, formate, mesylate, citrate, benzoate, fumarate, maleate, tartrate and succinate salts. In particular, sumatriptan succinate salt (1:1) may be used.

In one embodiment, sumatriptan granules may be prepared by dry blending sumatriptan with one or more diluents and/or binders and granulating the blend with a solvent. The solvent can be an aqueous and/or a non-aqueous solvent.

In another embodiment, sumatriptan granules may be prepared by granulating sumatriptan with an aqueous/non-aqueous solution/suspension of one or more diluents and/or binders.

In yet another embodiment, sumatriptan granules may be prepared by dry blending sumatriptan with a portion of the one or more diluents and/or binders and granulating the blend with an aqueous/non-aqueous solution/suspension of the remaining portion of the one or more diluents and/or binders.

In yet another embodiment, sumatriptan granules may be prepared by spraying an aqueous/non-aqueous solution/suspension of one or more diluents and/or binders over the sumatriptan particles.

In yet another embodiment, sumatriptan granules may be prepared by spraying an aqueous/non-aqueous solution/suspension of sumatriptan alone or in combination with one or more diluents and/or binders onto inert cores.

In yet another embodiment, sumatriptan granules may be prepared by spraying an aqueous/non-aqueous solution/suspension of sumatriptan alone or in combination with one or more diluents and/or binders onto inert cores. An additional layer of one or more diluents and/or binders then can be deposited (e.g., spray) onto the inert cores that have been encapsulated or layered wit the first layer.

The sumatriptan granules prepared above may be filled into capsules of suitable size as such, made into a dispersion, or additionally may be blended with one or more

pharmaceutically acceptable excipients and compressed into tablets or filled into capsules. The tablets or capsules optionally may be wax polished.

The optional wax polish includes a waxy material. Suitable waxy materials include one or more of shellac, modified shellac (opaglos), Opaglos II, carnuba wax, bees wax, paraffin wax, polyethylene glycol, and the like. One application is usually sufficient to obtain the desired effect. The preferred total weight build up of a wax polishing solid is up to about 10% w/w, based on the weight of the tablet.

Examples of suitable diluents useful for preparing sumatriptan granules include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and equivalents thereof.

Examples of suitable binders useful for preparing sumatriptan granules include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, alginate and equivalents thereof.

Examples of suitable disintegrants include one or more of hydroxypropyl cellulose, carboxymethylcellulose, calcium carboxymethylcellulose, sodium carboxymethylcellulose, croscarmellose sodium A-type (Ac-di-sol), starch, crystalline cellulose, hydroxypropyl starch, partly pregelatinized starch and equivalents thereof.

Examples of suitable lubricants/glidants include one or more of stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, silicon dioxide and equivalents thereof.

Examples of suitable coloring agents and flavoring agents include any FDA colors and flavors that are approved for oral use.

Examples of suitable inert cores include pharmaceutically acceptable inert cores available commercially or prepared from an inert material by processes of extrusion-spheronization, granulation and the like. Specific examples of commercially available inert cores include sugar spheres, non-pareil seeds, celpheres and the like. Alternatively, inert cores may be prepared from pharmaceutically acceptable inert soluble, insoluble and/or swellable materials, with or without pharmaceutically acceptable excipients. Examples of suitable soluble inert materials include sugars selected from glucose, mannitol, lactose, xylitol, dextrose, sucrose and equivalents thereof. Examples of suitable insoluble inert material include sand (silicon dioxide), glass, microcrystalline cellulose, plastic (polystyrene), and equivalents thereof. Examples of swellable inert material include hydroxypropyl methylcellulose and equivalents thereof. Inert cores may be of any geometric shape, although spherical cores are preferred for the ease of obtaining a uniform covering, layering or encapsulation.

Suitable solvents used for the preparation of sumatriptan granules may be selected from aqueous and/or non-aqueous solvents. Aqueous solvent used may be water whereas the non-aqueous solvent may be selected from one or more of ethanol, acetone, carbon tetrachloride, isopropyl alcohol, dichloromethane and equivalents thereof.

As described above and exemplified in more detail below, the process of forming taste masked sumatriptan dosage forms may be carried out by blending sumatriptan or its physiologically acceptable salts with approximately half of the quantity of one or more diluents and/or binders that are intended to be used; granulating the blend with the solvent; drying the granules and sifting to get the desired size; mixing the dried granules with rest of the one or more diluents and/or binders, and one or more disintegrants and/or lubricants; and compressing the blend to form tablets. Alternatively, sumatriptan may be granulated with the one or more diluents and/or binders dissolved or suspended in an appropriate solvent. These uncoated tablets optionally may be wax polished by spraying the wax solution or suspension using airless spray equipment. The wax polished tablets are either air dried or tray dried.

The following examples further exemplify the inventions and are not intended to limit the scope of the inventions.

Example 1

INGREDIENTS	QUANTITY(mg/tablet)
INTRAGRANULAR	
Sumatriptan Succinate eq. to 100 mg Sumatriptan	140.0
Lactose Monohydrate	133.0
Purified Water	q.s.
EXTRAGRANULAR	
Microcrystalline Cellulose	15.0
Croscarmellose Sodium.	3.0
Magnesium Stearate	3.0
Talc	6.0
TOTAL WEIGHT	**300.0**

Process for forming the tablets of Example 1:

1. Sumatriptan Succinate was sifted through a suitable mesh along with half of the above quantity of lactose and blended for 30 minutes to form a blend.
2. The blend was granulated using purified water to form granules.
3. The granules were dried at 60°C.
4. The dried granules were sized by passing them through a suitable mesh.
5. The sized granules were mixed with the remainder of the sifted lactose, the microcrystalline cellulose and the croscarmellose sodium for 20 minutes.
6. The granules formed in step 5 were mixed with magnesium stearate and talc for 5 minutes to form a blend.
7. The blend of step 6 was compressed using suitable tooling to form tablets.

The resulting tablets of Example 1 have an intragranular portion in which the sumatriptan is blended with the lactose monohydrate. The extragranular portion of the tablet partially or completely surrounds the granules.

Example 2

INGREDIENTS	QUANTITY (mg/tablet)
INTRAGRANULAR	
Sumatriptan Succinate Eq. to 100 mg Sumatriptan	140.0
Lactose Monohydrate	128.0
Purified Water	q.s.
EXTRAGRANULAR	
Microcrystalline Cellulose	32.5
Croscarmellose Sodium	6.0
Magnesium Stearate	4.5
Talc	3.0
Colloidal Anhydrous Silica	3.0
TOTAL WEIGHT	**300.0**

Process for forming the tablets of Example 2:

1. Lactose was dispersed in purified water.
2. Sumatriptan succinate was charged in a fluid bed processor and sprayed with the lactose dispersion by a top/bottom/tangential spray to obtain granules.
3. The granules were mixed with the remaining excipients and compressed to form tablets.

The resulting tablets of Example 2 have an intragranular portion in which the sumatriptan succinate is substantially or completely encapsulated with the lactose monohydrate. The extragranular portion of the tablet partially or completely surrounds the granules.

Example 3

INGREDIENTS	QUANTITY (mg/tablet)
INTRAGRANULAR	
Sumatriptan Succinate eq. to 100 mg Sumatriptan	140.0
Hydroxyproplyl Methylcellulose	20.0
Purified Water	q.s.
EXTRAGRANULAR	
Lactose Monohydrate	108.0
Microcrystalline Cellulose	32.5
Croscarmellose Sodium	6.0
Magnesium Stearate	4.5
Talc	3.0
Colloidal Anhydrous Silica	3.0
TOTAL WEIGHT	**300.0**

Process for forming the tablets of Example 3:

1. Hydroxypropyl methylcellulose was dispersed in purified water.
2. Sumatriptan succinate was charged in a fluid bed processor and sprayed with the hydroxypropyl methylcellulose dispersion by a top/bottom/tangential spray to obtain granules.
3. The granules were mixed with the remaining excipients and compressed to form tablets.

The resulting tablets of Example 3 have an intragranular portion in which the sumatriptan succinate is substantially or completely encapsulated by the hydroxypropyl methyl cellulose. The extragranular portion of the tablet partially or completely surrounds the granules.

Example 4

INGREDIENTS	QUANTITY (mg/tablet)
INTRAGRANULAR	
Nonpareil seeds	100.0
Sumatriptan Succinate eq. to 100 mg Sumatriptan	140.0
Lactose	100.0
Hydroxyproplyl Methylcellulose	20.0
Purified Water	q.s.
EXTRAGRANULAR	
Microcrystalline Cellulose	17.5
Croscarmellose Sodium	12.0
Magnesium Stearate	4.5
Talc	3.0
Colloidal Anhydrous Silica	3.0
TOTAL WEIGHT	**400.0**

Process for forming the tablets of Example 4:

1. Sumatriptan and lactose were dispersed in purified water.
2. Nonpareil seeds were charged in a fluid bed processor and sprayed with the sumatriptan and lactose dispersion by a top/bottom/tangential spray.
3. Hydroxypropyl methylcellulose was dispersed in purified water.
4. The hydroxypropyl methylcellulose dispersion was sprayed by a top/bottom/tangential spray on the coated nonpareil seeds.
5. The coated nonpareil seeds were mixed with the remaining excipients and compressed to form tablets.

The resulting tablets of Example 4 have an intragranular portion in which the sumatriptan succinate and the lactose are sprayed on the nonpareil seeds, which are

substantially or completely encapsulated with the hydroxypropyl methyl cellulose. The extragranular portion of the tablet partially or completely surrounds the granules.

The tablets prepared using the methods described in Examples 1-4 were optionally wax polished using any of the following techniques.

1. Carnuba Wax - 0.5 – 2.0 mg/tablet
   Process: The sumatriptan tablets were charged in a polishing pan, warmed to 40 - 45°C and sprinkled with fine powder grade of carnuba wax under rolling. The rolling was continued until uniform polishing was achieved.

2. Carnuba Wax - 0.5 – 2.0 mg/tablet
   Carbon tetrachloride - qs
   Process: The carnuba wax was dissolved in a sufficient quantity of carbon tetrachloride and the mixture was applied on the sumatriptan tablets in a polishing pan under a hot stream of air (40 – 45°C).

3. Polyethylene glycol - 0.5 – 2.0 mg/tablet
   Isopropyl alcohol – qs
   Methylene chloride – qs
   Process: Polyethylene glycol was dissolved in a solution containing equal amounts of isopropyl alcohol and methylene chloride and the resulting mixture was applied on the sumatriptan tablets in a polishing pan under a hot stream of air (40 – 45°C).

4. Carnuba Wax - 0.5 – 2.0 mg/tablet
   White wax - 0.25 – 1.0 mg/tablet
   Carbon tetrachloride – qs
   Process: Carnuba wax and white wax (2:1 preferred ratio) were dissolved in a sufficient quantity of carbon tetrachloride and the resulting mixture was applied on the sumatriptan tablets in a polishing pan under a hot stream of air (40 – 45°C).

5. Opaglos

   Process: The sumatriptan tablets were charged in a polishing pan and polished using Opaglos, to a desired amount.

The dosage forms described herein can be used to treat a mammal, such as a human, suffering from or susceptible to conditions associated with cephalic pain such as cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headaches associated with substances or their withdrawal (e.g., drug withdrawal), tension headache and, in particular, migraine headaches. The treatment involves oral administration of the pharmaceutical compositions described herein containing sumatriptan or a pharmaceutically acceptable salt or solvate thereof as the active ingredient. It should be understood that reference to treatment is intended to include prophylaxis as well as the treatment of expressed symptoms. The precise therapeutic dose of the active ingredient will depend on the age and condition of the patient and the nature of the condition to be treated. Moreover, the physician will have the discretion to vary the dose. In general, an effective dose for the treatment of conditions associated with cephalic pain, for example, acute treatment of migraine, is in the range of between 10 mg and 500 mg, particularly between 20 mg and 300 mg, and most particularly between 25 mg and 200 mg. For example, a suitable dose is a single or divided dose of 50 mg or 100 mg of the active ingredient per unit dose that is administered 1 to 4 times per day.

While several particular forms of the invention have been described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. For example, though only conventional dosage forms of sumatriptan are disclosed, a person skilled in the art, with proper selection of modified release polymers may easily reap the advantages of the invention and hence would come within the scope of this invention. Modified release dosage forms may be prepared by using one or more modified release polymers. Examples of modified release polymers include cellulose derivatives such as ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methyl cellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose triacetate, agar acetate, amylose acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulphonate, cellulose acetate butyl sulphonate, cellulose acetate propionate, cellulose acetate diethylamino-acetate, cellulose acetate octate, cellulose acetate laurate, cellulose acetate p-

toluenesulphonate, cellulose acetate butyrate; waxes such as polyethylene glycols; polymeric epoxides; copolymers of alkylene oxides and alkyl glycidyl ethers; polyglycols or polylactic acid derivatives; polysaccharides such as xanthan gum, guar gum, alginic acid; acrylic polymers such as eudragits and carbopols; and the like.

It may also be possible for a person skilled in the art to polish the dosage form using waxy materials other than those disclosed and they are thus expected to fall within the scope of this application. Moreover, the granules formed above can be filled into a capsule or made into another dosage form, such as a dispersion in a suitable medium.

A second active pharmaceutical ingredient can be used intragranularly, extragranularly, or both, provided the active pharmaceutical ingredients are chemically compatible to each other in the dosage form so prepared. For example, the sumatriptan of Example 1 can be granulated with a second active pharmaceutical ingredient. Alternatively, granules of the second active ingredient may be prepared separately and then the two types of granules may be blended together with extragranular excipients and compressed into tablets or filled into capsules.

The lactose of Example 2 can be mixed with a second active pharmaceutical ingredient and sprayed with the lactose onto the sumatriptan. Similarly, the hydroxypropyl methyl cellulose of Example 3 can be dispersed with a second active pharmaceutical ingredient and sprayed onto the sumatriptan. Moreover, based on the details of either Example 2 or 3, a blend of sumatriptan and a second active ingredient may be charged in a fluidized bed processor over which lactose/hydroxypropyl methylcellulose dispersion is sprayed. The second active ingredient also may be mixed with lactose in the dispersion and sprayed over sumatriptan. Further, as described above, the second active ingredient may be processed separately to prepare granules following the processes of Example 2 or 3 and finally the two different types of granules may be combined to prepare the dosage form.

The dispersion of sumatriptan and lactose of Example 4 and/or the dispersion of hydroxypropyl methyl cellulose of Example 4 can further include additional active pharmaceutical ingredients and be sprayed onto the seed and/or coated seed. Alternatively, the second active ingredient may be applied as a dispersion in a separate layer. Further, as in the examples above, the second active ingredient may be processed separately to prepare

granules and finally the two different types of coated non pareils may be combined to prepare the dosage form.

An example of a suitable active pharmaceutical ingredient for administration with sumatriptan includes analgesics, such as ibuprofen, Tylenol®, and APAP (Acetaminophen). Moreover, other active pharmaceutical ingredients can be processed as described above to taste mask those ingredients. These active pharmaceutical ingredients include: antibiotics, such as penicillins, amoxicillin, and amoxicillin alone or in combination with clavulanic acid or clavulanic acid in the form of a potassium salt; penicillin V and therapeutically active derivatives, e.g., oxacillin, cloxacillin, flucoxacillin, dicloxacillin, and ampicillin; cephalosporins, e.g., cefaclor, cefixime, cephalexin, cephradine, cefadroxil, cefroxadine, cefdinir, cefpodoxime proxetil, and cefuroxime axetil; macrolides, e.g., erythromycin A, clarithromycin, azithromycin, and roxithromycin; antimigraines; and antipsychotics such as olanzapine. Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

WE CLAIM:

1. A process for preparing an uncoated sumatriptan tablet for oral administration, the process comprising the steps of:

granulating sumatriptan or a pharmaceutically acceptable salt with one or more diluents and/or binders to form granules;

mixing the granules with one or more pharmaceutically acceptable excipients to form a mixture; and

compressing the mixture to form a tablet.

2. The process according to claim 1, further comprising wax polishing the tablet.

3. The process according to claim 1, wherein granulating comprises dry mixing the one or more diluents and/or binders with sumatriptan and granulating with an aqueous and/or a non-aqueous solvent.

4. The process according to claim 1, wherein the sumatriptan is granulated with an aqueous and/or a non-aqueous solution or a suspension of one or more diluents and/or binders.

5. The process according to claim 3 or 4, wherein the aqueous solvent comprises water.

6. The process according to claim 3 or 4, wherein the non-aqueous solvent comprises one or both of alcohol and isopropyl alcohol.

7. The process according to claim 1, wherein the pharmaceutically acceptable salt comprises one or more of hydrochloride, hydrobromide, sulphate, nitrate, phosphate, formate, mesylate, citrate, benzoate, fumarate, maleate, tartrate and succinate salts.

8. The process according to claim 7, wherein the pharmaceutically acceptable salt comprises succinate (1:1).

9. The process according to claim 1, wherein the one or more diluents comprises one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic,

calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, and sugar confectioners.

10. The process according to claim 9, wherein the diluent comprises lactose.

11. The process according to claim 1, wherein the binder comprises one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and alginate.

12. The process according to claim 11, wherein the binder comprises hydroxypropyl methylcellulose.

13. The process according to claim 1, wherein the pharmaceutically acceptable excipient comprises one or more of diluents, binders, disintegrants, lubricants, coloring agents, and flavoring agents.

14. The process according to claim 13, wherein the disintegrant comprises one or more of low substituted hydroxypropyl cellulose, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, croscarmellose sodium, starch, crystalline cellulose, hydroxypropyl starch, and partially pregelatinized starch.

15. The process according to claim 14, wherein the disintegrant comprises croscarmellose sodium.

16. The process according to claim 14, wherein the lubricant comprises one or more of stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated caster oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, and white beeswax.

17. The process according to claim 16, wherein the lubricant comprises one or both of talc and magnesium stearate.

18. The process according to claim 2, wherein the wax polishing comprises spraying a solution or suspension of wax onto the tablet.

19. The process according to claim 2, wherein the wax polishing comprises sprinkling a powder grade wax onto the tablet.

20. The process according to claim 2, wherein wax material comprises one or more of shellac, modified shellac, opaglos II, carnuba wax, bees wax, paraffin wax, and polyethylene glycol.

21. The process according to claim 20, wherein the wax material comprises modified shellac.

22. The process according to claim 2, wherein the total weight build up of wax polishing solid comprises up to about 10% w/w, based on the total weight of the tablet.

23. The process according to claim 1, further comprising granulating and/or mixing a second active pharmaceutical ingredient with the sumatriptan.

24. A process for preparing uncoated sumatriptan tablets for oral administration, the process comprising the steps of:

spraying a solution or suspension of sumatriptan or a pharmaceutically acceptable salt in a solvent onto inert cores to form a first layer;

blending the core having the first layer with one or more pharmaceutically acceptable excipients to form a blend; and

compressing the blend to form a tablet.

25. The process of claim 24, wherein the solution or suspension of sumatriptan in a solvent further includes one or more diluents and/or binders.

26. The process of claim 24, further comprising creating a second layer on the cores having the first layer, the second layer comprising one or more diluents and/or binders.

27. The process of claim 25, further comprising creating a second layer on the cores having the first layer, the second layer comprising one or more diluents and/or binders.

28. The process of claim 24, further comprising polishing the tablet.

29. The process of claim 28, wherein polishing the tablet comprises sprinkling a fine powder grade of a wax material on the tablet.

30. The process of claim 28, wherein polishing the tablet comprises spraying a solution or suspension of a wax material in organic solvent onto the tablet.

31. The process according to claim 24, wherein the inert core comprises one or more of a sugar sphere, a non-pareil seed, celpheres, or a pharmaceutically acceptable inert insoluble, soluble or swellable material.

32. The process according to claim 31, wherein the pharmaceutically acceptable inert core comprises a non-pareil seed.

33. The process according to claim 31, wherein the insoluble inert material comprises one or more of sand, silicon dioxide, glass, microcrystalline cellulose, a plastic, and polystyrene.

34. The process according to claim 31, wherein the soluble inert material comprises one or more of a sugar, glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

35. The process according to claim 31, wherein the swellable inert material comprises hydroxypropyl methylcellulose.

36. The process according to claim 24, further comprising spraying and/or blending a second active pharmaceutical ingredient with the sumatriptan.

37. A wax polished dosage form of sumatriptan, the dosage form comprising:

sumatriptan or a pharmaceutically acceptable salt;

one or more pharmaceutically acceptable carriers or excipients; and

a wax polish on the dosage form.

38. The wax polished dosage form of sumatriptan of claim 37, wherein the wax polish comprises a wax material.

39. The wax polished dosage form of sumatriptan of claim 37, wherein the wax material comprises one or more of shellac, modified shellac, opaglos II, carnuba wax, bees wax, paraffin wax, polyethylene glycol.

40. The wax polished dosage form of sumatriptan of claim 37, wherein the total weight buildup of wax material is up to 10% w/w, based on the weight of tablet.

41. The wax polished dosage form of sumatriptan of claim 37, wherein the dosage form is a tablet or capsule.

42. The wax polished dosage form of sumatriptan of claim 37, wherein the dosage form is a tablet.

43. The wax polished dosage form of sumatriptan of claim 37, wherein the one or more pharmaceutically acceptable excipients includes one or more of diluent, binder, disintegrant, lubricant/glidant, coloring agent and flavoring agent.

44. The wax polished dosage form of sumatriptan of claim 37, further comprising a second active pharmaceutical ingredient in the dosage form.

45. An uncoated, wax polished sumatriptan tablet comprising:

a tablet core comprising about 10-200 mg of sumatriptan or a physiologically acceptable salt and one or more pharmaceutically acceptable carriers or excipients, and

a wax polish on the tablet core,

wherein the wax polish comprises an amount of from about 2 to 10% weight/weight of the tablet.

46. An uncoated, taste-masked sumatriptan tablet for oral administration, the uncoated tablet comprising:

an intragranular portion comprising granules of sumatriptan or a pharmaceutically acceptable salt and one or more diluents and/or binders present in a sufficient amount to cause taste-masking of the sumatriptan or pharmaceutically acceptable salt; and

an extragranular portion comprising one or more pharmaceutically acceptable excipients around the intragranular granules.

47. The uncoated, taste-masked sumatriptan tablet of claim 46, wherein the one or more diluents and/or binders in the intragranular portion completely encapsulate the sumatriptan or physiologically acceptable salt.

48. The uncoated, taste-masked sumatriptan tablet of claim 46, wherein the one or more diluents and/or binders in the intragranular portion substantially encapsulate the sumatriptan or physiologically acceptable salt.

49. The uncoated, taste-masked sumatriptan tablet of claim 46, wherein the intragranular portion and/or the extragranular portion further comprises a second active pharmaceutical ingredient.

50. A method of treating or prophylactically treating a human suffering from a migraine condition, the method comprising orally administering a wax polished dosage form of sumatriptan, the oral dosage form comprising:

sumatriptan or a physiologically acceptable salt and a pharmaceutically acceptable carrier or excipient;

one or more pharmaceutically acceptable carriers or excipients; and

a wax polish on the dosage form.

51. The method of treating of claim 50, wherein the tablet comprises about 10 mg to 200 mg of sumatriptan.

52. A method of treating or prophylactically treating a human suffering from a migraine condition, the method comprising orally administering an uncoated, taste-masked tablet of sumatriptan, the uncoated tablet comprising:

an intragranular portion comprising granules of sumatriptan or a pharmaceutically acceptable salt and one or more diluents and/or binders present in a sufficient amount to cause taste-masking of the sumatriptan or pharmaceutically acceptable salt; and

an extragranular portion comprising one or more pharmaceutically acceptable excipients around the intragranular granules.

53. The method of treating of claim 52, wherein the tablet comprises about 10 mg to 200 mg of sumatriptan.

54. The method of treating of claim 52, wherein the intragranular portion and/or the extragranular portion further comprises a second active pharmaceutical ingredient.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

10/521402

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 January 2004 (29.01.2004)

PCT

(10) International Publication Number
WO 2004/009085 A3

(51) International Patent Classification[7]: A61K 31/4045, 9/20, 9/28

(21) International Application Number: PCT/IB2003/002838

(22) International Filing Date: 17 July 2003 (17.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
759/DEL/2002 19 July 2002 (19.07.2002) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, 110 019 New Delhi, Delhi (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MATHUR, Rajeev, Shankar** [IN/IN]; KD-66, A, Ashok Vihar Phase - 1, 110052 Delhi (IN). **KUMAR, T. Vijaya** [IN/IN]; H. No. 7-150, Main Raod, Chagalamarry, Dist - Kurnool, 518553 Andhra Pradesh (IN). **ROY, Sunilendu, Bhushan** [IN/IN]; Bungalow #7, Row House, Lokpuram, Thane (West), Mumbai, 400601 Maharashtra (IN). **MALIK, Rajiv** [IN/IN]; 6-B, Pocket-B, Gangotri Enclave, Alaknanda, 110019 New Delhi, Delhi (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay. R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
13 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/009085 A3

(54) Title: TASTE MASKED SUMATRIPTAN TABLETS AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The technical field of the present invention relates to uncoated, taste masked sumatriptan tablets for oral administration and processes for their preparation. It also relates to wax polished sumatriptan tablets and processes for their preparation.

INTERNATIONAL SEARCH REPORT

PCT/EB 03/02838

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4045 A61K9/20 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/037816 A (BIOCHEMIE GMBH ;ENTNER REINHARD (AT); JENNEWEIN HERWIG (AT)) 31 May 2001 (2001-05-31) cited in the application the whole document example 1 page 2, lines 4-15	1,3-17, 23, 46-49, 52-54
X	EP 0 503 440 A (GLAXO GROUP LTD) 16 September 1992 (1992-09-16) the whole document example 1 page 2, lines 32-44 page 3, lines 3-31 page 3, line 5355	1,3-17, 23, 46-49, 52-54

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 2003	20. 02. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Luangkhot, N

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
	& US 5 863 559 A 26 January 1999 (1999-01-26) cited in the application	
X	WO 01/003672 A (BRUNA ETIENNE ;PROGRAPHARM LAB (FR); CHAUVEAU CHARLES (FR); NOURI) 18 January 2001 (2001-01-18) the whole document example 1 page 1, lines 26-30 page 3, lines 1-26 page 5, lines 16,17 page 11, lines 6-15 claims 1-21	1,3-17, 23, 46-49, 52-54
P,X	WO 03/053402 A (COX STEVE R ;HEIMLICH JOHN M (US); JOHN LEE E (US); NOACK ROBERT M) 3 July 2003 (2003-07-03) the whole document page 4, lines 27-34 page 11, lines 6-24 examples 1-3 claims 1-4,8-17	1,3-17, 23, 46-49, 52-54
E	WO 03/075893 A (ROSENBERGER VERED ;AQUA OFER (IL); TEVA PHARMA (IL); LERNER E ITZH) 18 September 2003 (2003-09-18) the whole document page 1, lines 12-15 page 4, lines 1-11 page 37; example 5 claims 1,2,4,32-39	1,3-17, 23, 46-49, 52-54
A	WO 98/06932 A (ADVANCED ENGINE TECH PTY LTD ;MANTHEY STEVEN CHARLES (AU)) 19 February 1998 (1998-02-19) the whole document	1
A	WO 00/48583 A (POZEN INC) 24 August 2000 (2000-08-24) the whole document	1

INTERNATIONAL SEARCH REPORT

PCT/IB 03/02838

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 2,18-22,28-30
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 52-54 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 2,18-22,28-30
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 3-17, 23, 46-49, 52-54

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 2,18-22,28-30

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

---

Continuation of Box I.2

Claims Nos.: 2,18-22,28-30

Claims 2,18-22 and 28-30 do not meet the requirement of Art.6 PCT for lack of clarity because they are directed to a subject-matter (process comprising further the step of polishing the tablet with wax) which is in contradiction with the subject-matter of their independent claims (process of producing uncoated tablet), namely inventions 1 and 3.

The step of wax polishing in claims 2,18-22 and 28-30 belongs in fact to the subject-matter of invention 2, which will be searched when the fees are paid. Therefore even if they depend prima facea on claims 1 or 24, they will not be searched within the frame of the search of the first invention.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 3-17, 23, 46-49, 52-54

Process for manufacturing a sumatriptan tablet comprising:
1/ manufacturing granules of sumatriptan with diluents or binders
2/ mixing the obtained granules with other excipients in order to obtain a mixture or an extragranular portion
3/ compressing the product of step 2 in order to form a tablet

---

2. claims: 37-44, 45, 50-51

Process for manufacturing a sumatriptan dosage form comprising wax polishing the dosage form

---

3. claims: 24-25, 26-27, 31-36

Process for manufacturing a sumatriptan tablet comprising:
1/ spraying a solution or suspension of sumatriptan onto inert cores, and optionally further spraying a solution of binders or diluents onto the cores having the first layer (claims 26-27)
2/ mixing the product of step 1 with other excipients in order to form a mixture
3/ compressing the mixture to form a tablet

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5863559 A		AT 165973 T	15-05-1998
		AU 1326492 A	06-10-1992
		BE 1005086 A5	13-04-1993
		CH 684242 A5	15-08-1994
		CY 2011 A	20-02-1998
		DE 69225421 D1	18-06-1998
		DE 69225421 T2	15-10-1998
		DK 503440 T3	18-01-1999
		WO 9215295 A1	17-09-1992
		EP 0503440 A1	16-09-1992
		ES 2117015 T3	01-08-1998
		FR 2673538 A1	11-09-1992
		GB 2254784 A ,B	21-10-1992
		HK 19395 A	17-02-1995
		IE 920726 A1	09-09-1992
		IL 101162 A	20-11-1997
		IT 1271495 B	30-05-1997
		MX 9200992 A1	01-09-1992
		NL 9200423 A	01-10-1992
		NZ 241873 A	27-06-1994
		OA 9812 A	15-04-1994
		SG 169294 G	28-04-1995
		ZA 9201690 A	02-08-1993
WO 0103672 A	18-01-2001	FR 2795962 A1	12-01-2001
		AU 760006 B2	08-05-2003
		AU 5993600 A	30-01-2001
		BG 106398 A	30-09-2002
		BR 0012250 A	26-03-2002
		CA 2375600 A1	18-01-2001
		CN 1373658 T	09-10-2002
		CZ 20020018 A3	17-04-2002
		EA 3161 B1	27-02-2003
		EP 1194125 A1	10-04-2002
		WO 0103672 A1	18-01-2001
		HU 0202062 A2	28-12-2002
		JP 2003504324 T	04-02-2003
		NO 20016308 A	21-12-2001
		NZ 516594 A	28-11-2003
		SK 19392001 A3	04-04-2002
		TR 200200013 T2	21-06-2002
		US 2002098227 A1	25-07-2002
		ZA 200200344 A	15-01-2003
WO 03053402 A	03-07-2003	WO 03053402 A1	03-07-2003
		US 2003133982 A1	17-07-2003
		WO 03053420 A1	03-07-2003
		US 2003129236 A1	10-07-2003
WO 03075893 A	18-09-2003	WO 03057136 A2	17-07-2003
		WO 03075893 A1	18-09-2003
		US 2003206954 A1	06-11-2003
WO 9806932 A	19-02-1998	AU 713036 B2	18-11-1999
		AU 3689597 A	06-03-1998
		WO 9806932 A1	19-02-1998
		BG 63578 B1	31-05-2002
		BG 103157 A	30-09-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9806932 A		BR 9711049 A	17-08-1999
		CA 2263332 A1	19-02-1998
		CN 1255184 A ,B	31-05-2000
		CZ 9900426 A3	16-06-1999
		EA 1670 B1	25-06-2001
		EP 0917617 A1	26-05-1999
		HK 1028093 A1	01-08-2003
		HU 9903167 A2	28-02-2000
		IL 128422 A	23-05-2002
		JP 2000516316 T	05-12-2000
		KR 2000029881 A	25-05-2000
		NO 990584 A	09-04-1999
		NZ 334134 A	29-04-1999
		PL 331510 A1	19-07-1999
		US 6155214 A	05-12-2000
WO 0048583 A	24-08-2000	AU 3596500 A	04-09-2000
		WO 0048583 A2	24-08-2000
		US 6586458 B1	01-07-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0137816 A	31-05-2001	AU 2358501 A	04-06-2001
		BR 0015449 A	09-07-2002
		CA 2387575 A1	31-05-2001
		CN 1391465 T	15-01-2003
		CZ 20021765 A3	14-08-2002
		WO 0137816 A2	31-05-2001
		EP 1231903 A2	21-08-2002
		HU 0204072 A2	28-05-2003
		JP 2003514848 T	22-04-2003
		NO 20022362 A	11-07-2002
		SK 6962002 A3	08-10-2002
		TR 200201028 T2	21-10-2002
EP 0503440 A	16-09-1992	AT 165973 T	15-05-1998
		AU 663303 B2	05-10-1995
		AU 1326492 A	06-10-1992
		BE 1005086 A5	13-04-1993
		CA 2105180 A1	09-09-1992
		CH 684242 A5	15-08-1994
		CZ 9301849 A3	15-06-1994
		CY 2011 A	20-02-1998
		DE 69225421 D1	18-06-1998
		DE 69225421 T2	15-10-1998
		DK 503440 T3	18-01-1999
		WO 9215295 A1	17-09-1992
		EP 0503440 A1	16-09-1992
		ES 2117015 T3	01-08-1998
		FR 2673538 A1	11-09-1992
		GB 2254784 A ,B	21-10-1992
		HK 19395 A	17-02-1995
		IE 920726 A1	09-09-1992
		IL 101162 A	20-11-1997
		IT 1271495 B	30-05-1997
		JP 2986546 B2	06-12-1999
		JP 6505020 T	09-06-1994
		KR 202042 B1	15-06-1999
		MX 9200992 A1	01-09-1992
		NL 9200423 A	01-10-1992
		NZ 241873 A	27-06-1994
		OA 9812 A	15-04-1994
		RU 2098093 C1	10-12-1997
		SG 169294 G	28-04-1995
		US 2002197318 A1	26-12-2002
		US 6020001 A	01-02-2000
		US 5863559 A	26-01-1999
		US 6368627 B1	09-04-2002
		ZA 9201690 A	02-08-1993
US 5863559 A	26-01-1999	US 2002197318 A1	26-12-2002
		US 6020001 A	01-02-2000
		US 6368627 B1	09-04-2002
		AU 663303 B2	05-10-1995
		CA 2105180 A1	09-09-1992
		CZ 9301849 A3	15-06-1994
		JP 2986546 B2	06-12-1999
		JP 6505020 T	09-06-1994
		KR 202042 B1	15-06-1999
		RU 2098093 C1	10-12-1997